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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,073	02/28/2005	Shigekazu Hokazono	HOKAZONO1	8315

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,073	HOKAZONO ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *2-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: alignments

DETAILED ACTION

Status of the Application

Claims 1-6 are pending.

Applicant's election with traverse of Group I, claims 1 and 6, drawn to a polypeptide having thermostable ribonuclease H activity as submitted in a communication filed on 6/29/2007 is acknowledged.

Applicant traverses on the grounds that the ribonuclease H of Itaya et al. is not the same as that claimed in the instant application.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. As indicated in the restriction requirement mailed on 6/1/2001, claim 1 encompasses not only the polypeptide of SEQ ID NO: 1 but it also encompasses any thermostable ribonuclease H as indicated in item (b) of that claim. It is reiterated herein that a polypeptide having thermostable ribonuclease H activity which is a variant of the polypeptide of SEQ ID NO: 1 that results from any number of modifications (i.e., at least one amino acid residue deleted, added, inserted, or substituted) is essentially a thermostable ribonuclease H which can have any structure. As such, the technical feature linking the inventions of Groups I and II is a thermostable ribonuclease H, wherein said ribonuclease H can have any structure. Since Itaya et al. teach a thermostable ribonuclease H from *T. thermophilus* HB8, the technical feature linking the two groups does not make a contribution over the prior art, the claimed inventions do not meet the requirement of unity of invention under PCT Rule 13.2.

The requirement is deemed proper and therefore is made FINAL.

Claims 2-5 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1 and 6 are at issue and are being examined herein.

Specification

1. The abstract of the disclosure is objected to because it is not sufficiently descriptive. See MPEP § 608.01(b). The content of a patent abstract should be such as to enable the reader thereof, regardless of his or her degree of familiarity with patent documents, to determine quickly from a cursory inspection of the nature and gist of the technical disclosure and should include that which is new in the art to which the invention pertains. In the instant case, the abstract is not sufficiently descriptive of the invention claimed because it does not provide any indication as to the enzyme's source. Appropriate correction is required.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. It is suggested that the name of the organism from which the enzyme was isolated be included in the title. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to JAPAN 2002-254153 filed on 08/30/2002.

4. The instant application is the US National stage of PCT/JP03/10727 filed on 08/26/2003.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 5/31/2005 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

6. The drawings submitted on 2/28/2005 have been reviewed and are accepted by the Examiner for examination purposes.

Claim Objections

7. Claim 1 is objected to due to the recitation of "polypeptide having an amino acid sequence in which at least one amino acid residue is deleted, added, inserted or substituted in the amino acid sequence of SEQ ID NO: 1". For clarity and consistency with commonly used claim language, it is suggested the term be amended to recite, for example, "a variant of the polypeptide of SEQ ID NO: 1, wherein said variant is obtained by deleting, adding, inserting or substituting at least one amino acid in the polypeptide of SEQ ID NO: 1". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claim 1 is indefinite in the recitation of "54% homology" because the term is unclear and confusing in the absence of a definition providing the intended meaning of the term "homology" or the intended parameters required to determine the required homology value. While one could argue that the term "sequence homology" can be interpreted as "sequence identity", as known in the art, these terms are not equivalent. The calculation of sequence homology takes into consideration the type of mismatches, i.e. even mismatches contribute to the % homology value, whereas mismatches do not have any weight in the calculation of sequence identity, i.e. only exact matches contribute to the % identity value. Thus, if

there is no indication that the term "homology" is intended to mean "identity", and the specification does not provide the specific parameters intended in the calculation of sequence homology (e.g., BLOSUM62), one of skill in the art cannot determine the scope of the term "54% homology" because one could have a polypeptide which is 54% sequence homologous to a reference sequence based on a particular matrix, and at the same time not 54% sequence homologous to the same reference sequence if other matrices and/or parameters are used. For examination purposes, it will be assumed that the term "54% homology" refers to any homology calculated by any method. Correction is required.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 1 and 6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1 and 6, as written, do not sufficiently distinguish over proteins as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring product. It is noted that while claim 6 recites the limitation "obtainable by culturing a transformant...", the term "obtainable" in its broadest reasonable interpretation is equivalent to "can be obtained". As such, claim 6 is not limited to a recombinant polypeptide. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by pages 31-32 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, First Paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As stated in MPEP 2111.01, during examination, the claims must be interpreted as broadly as their terms reasonably allow. As indicated above, claim 1(b) encompasses a variant of the polypeptide of SEQ ID NO:1 having any number of amino acid modifications. In addition, claim 1(c) as interpreted encompasses any thermostable ribonuclease H having any structural homology to the polypeptide of SEQ ID NO: 1. Therefore, claim 1 is directed in part to a genus of thermostable ribonucleases H having either any structure or essentially any structure. Claim 6 is also directed in part to a genus of thermostable ribonucleases H having any structure in view of the fact that the term "obtainable" is equivalent to "can be obtained", thus encompassing any thermostable ribonuclease H obtained by other means. See Claim Rejections under 35 USC 112, second paragraph.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other

physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

There is either no structural limitation (claims 1(b) and 6) or essentially no structural limitation (claim 1(c)) with regard to the members of the genus of proteins recited. While the specification in the instant application discloses the structure of the polypeptide of SEQ ID NO: 1, it provides no information as to the structural elements required in any polypeptide having thermostable ribonuclease H activity, nor does it teach which structural elements within the polypeptide of SEQ ID NO: 1 are required to display the recited activity.

The claims encompass an extremely large genus of proteins which is structurally unrelated. A sufficient written description of a genus of proteins may be achieved by a recitation of a representative number of proteins defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, either there is no structural feature recited, or the structural feature recited/interpreted, i.e., any structural homology to the polypeptide of SEQ ID NO: 1, does not constitute a substantial portion of the genus as the remainder of the structure of any polypeptide having thermostable ribonuclease H activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. Furthermore, while one could argue that the polypeptide of SEQ ID NO: 1 is representative of the structure of all the members of the genus of proteins recited, it is noted that the art teaches several examples of how even small structural variations can lead to functional variation. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teach that one

conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teach that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the recited activity has been provided, one cannot reasonably conclude that the structures disclosed are representative of all the proteins recited.

Due to the fact that the specification only discloses a single species of the genus of proteins recited, i.e., SEQ ID NO:1, as well as the lack of description of additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

15. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention of claim 6 requires a novel vector. Since the vector is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The recited vector's sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the vector. The specification does not disclose a repeatable process to obtain the vector and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of this plasmid should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that the specification indicates that Applicant has deposited an organism comprising the vector but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain containing the organism comprising the vector has been deposited under the Budapest Treaty and that the organism will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, applicants may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;
b. upon granting of the patent the organism will be available to the public under the conditions specified in 37 CFR 1.808;
c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
d. the deposit will be replaced if it should ever become unviable.

16. Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 1, does not reasonably provide enablement for any thermostable ribonuclease H having any structure or having any structural homology to the polypeptide of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence

and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breadth of the claims. Claims 1 and 6 are so broad as to encompass any thermostable ribonuclease H or any thermostable ribonuclease H which is structurally homologous to the polypeptide of SEQ ID NO:1. See Claim Rejections under 35 USC 112, first and second paragraph, for claim interpretation and discussion of scope. The enablement provided is not commensurate in scope with the claims due to the lack of information as to the structural features required by a polypeptide to have thermostable ribonuclease H activity. The teachings of the specification enable the polypeptide of SEQ ID NO:1, as well as compositions comprising said polypeptides.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the amino acid sequence of the polypeptide of SEQ ID NO: 1 as a working example. However, the specification fails to provide any clue as to (1) the structural elements within the polypeptide of SEQ ID NO: 1 which are essential for any protein to display the recited activity, or (2) a correlation between structure and the recited activity.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any thermostable ribonuclease H. In addition, the art does not provide any teaching or guidance as to (1) which amino acids within the polypeptide of SEQ ID NO: 1 can be modified and which ones are to be conserved such that one of skill in the art can make variants as recited with the same biological activity as that of the polypeptide of SEQ ID NO: 1, (2) which segments of the polypeptide of SEQ ID NO: 1 are

essential for activity, and (3) the general tolerance of thermostable ribonucleases H to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. and Seffernick et al. already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for an essentially infinite number of proteins and determine which ones have the recited activity. It is not routine in the art to isolate/create any protein with the recited activity without any knowledge as to the structural features which would correlate with that activity. In the absence of (1) a rational and predictable scheme for modifying any amino acid in the polypeptide of SEQ ID NO: 1 such that the resulting variant would have thermostable ribonuclease H activity, and/or (2) a correlation between structure and activity, one of skill in the art would have to test a virtually infinite number of polypeptides to determine which ones have the recited activity. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must

provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Itaya et al. (Nucleic Acids Research 19(16):4443-4449, 1991; cited in the IDS). Claims 1 and 6 are directed in part to a thermostable ribonuclease H having any structure. See Claim Rejections under 35 USC 112, first and second paragraphs, for claim interpretation and discussion of scope. Itaya et al. teach a thermostable ribonuclease H from *T. thermophilus* HB8 (Figure 1; page 4447, Structure of the *T. thermophilus* RNase H protein). Thus, the teachings of Itaya et al. anticipate the instant claims as written.

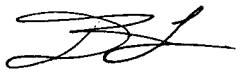
19. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Klenk et al. (PIR accession number E69327, 1997). Klenk et al. teach an *Archaeoglobus fulgidus* thermostable ribonuclease H having 53% sequence identity to the polypeptide of SEQ ID NO:1 (53% = 112x100/211) and 54.3% sequence homology to the polypeptide of SEQ ID NO: 1 using BLOSUM100 as the comparison matrix (Gap open penalty = 5 and Gap extension penalty = 4; see attached alignments). Claims 1 and 6 are directed in part to a thermostable ribonuclease H having any structure. Claim 1 is also directed in part to a thermostable ribonuclease H which is at least 54% sequence homologous to the polypeptide of SEQ ID NO: 1. See Claim Rejections under 35 USC 112, first and second paragraphs, for claim interpretation and discussion of scope. Therefore, the *Archaeoglobus fulgidus* thermostable ribonuclease H of Klenk et al. anticipates the instant claims as written.

Conclusion

20. No claim is in condition for allowance.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Primary Patent Examiner
Art Unit 1652

August 28, 2007